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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,803	02/05/2001	Vanitha Ramakrishnan	044481-5044	3916

9629 7590 01/30/2002  
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WASHINGTON, DC 20004

EXAMINER

WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
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1633

DATE MAILED: 01/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/775,803

Applicant(s)

RAMAKRISHNAN ET AL.

Examiner

Brian Whiteman

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-- Th MAILING DATE of this communication appears on th cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 October 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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## **DETAILED ACTION**

### **Non-Final Rejection**

The specification has been amended by the preliminary amendment in paper no. 7A filed on 12/13/01 with no new matter being added.

#### ***Priority***

Priority to provisional application 60/109,797 filed on 8/4/1998 is acknowledged.

#### ***Oath/Declaration***

The petition filed on 10/9/01 for filing an application under 37 CFR 1.47(a) is acknowledged.

#### ***Claim Objections***

Claim 1, 5, 10, 15, 23 are objected to because of the following informalities: the word "glycoprotein" should precede the abbreviation "GP" in any independent claim. Claim 23 is objected to for reciting a grammatically improper phrase, "An cell." Step c in Claim 10 is referring to itself. Appropriate correction is required.

#### ***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-27 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility due to its not being supported by either specific and/or substantial utility or a well-established utility.

Definitions: [from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS:

repeated from <http://www.uspto.gov/web/menu/utility.pdf>]

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“Credible Utility” – Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being “wrong”. Rather, office personnel must determine if the assertion of utility is credible (i.e. whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

“Specific utility” – a utility that is *specific* to the subject matter claimed. This contrast with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a “gene probe” or “chromosome marker” would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what conditions can be diagnosed.

“Substantial utility” – a utility that defines a “real world” use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a “substantial utility” define a “real world” context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a “real world” context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use and, therefore, do not define “substantial utilities”:

- A. Basic Research such as studying the properties of the claimed produce itself or the mechanisms in which the material is involved.
- B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)
- C. A method of assaying for or identifying a material that itself has no “specific and/or substantial utility”.
- D. A method of making a material that itself has no specific, substantial and credible utility.
- E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that “throw away” utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a “real world” context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are “throw away” utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. 101. This analysis should of course, be tempered by consideration of the context and nature of the invention. For example, if a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

“Well established utility” – a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification’s disclosure of the properties of a material, alone, or taken with the knowledge of one skilled in the art. “Well established utility” does not encompass any “throw away” utility that one can dream up for an invention or a non-specific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this were the case, any product or apparatus, including perpetual motion machines, would have a “well established utility” as landfill, an amusement device, a toy, or a paper weight, any carbon containing molecule would have a “well established utility” as a fuel since it can be burned; and any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.

[See also the MPEP at 2107–2107.02].

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The specification displays a method of generating a transgenic non-human mouse, wherein the steps comprise: a DNA sequence encoding GPV comprising a coding region of mouse GPV (including the putative initiator Met to Leu<sup>389</sup>) was replaced by a neo cassette and injected the vector into an ES cell line (pages 14-15). The neo clones were identified by positive selection and the clones were injected into embryos from C57BL/6J mice (page 15). Furthermore, the disclosure provides characterization of the effect of GPV gene deletion on thrombin-induced platelet function at low concentrations of thrombin (Example 5, pages 22-23). Furthermore, in example 6, the specification displays the GP V<sup>-/-</sup> mice have a decrease bleeding time in vivo compared to +/+ mice and +/- GPV mice (page 23-24). The specification contemplates that the transgenic mice can be used in a method for identifying agents that modulate a biological response (e.g. thrombotic or pro-thrombotic) (pages 25). More specifically, on pages 24-25 of the disclosure, the specification displays that based on the working examples, the GP V gene may have several biological functions a) Cleavage of GP V may be essential for the activation of the platelet by the subsequent generation of an intracellular signal which results in the inside-out activation of GPIIb-IIIa, b) GP V may function as an analogous to a brake with cleavage of GP V allowing platelet activation via signaling through the GPIb-IX complex, and inside out activation of GPIIb-IIIa, c) Role in coagulation, since the cleavage of GP V occurs at concentrations of thrombin much lower than that required to cleave other platelet surface proteins, GP V cleavage may be part of the process which occur in arteries which culminates in the formation of a thrombus. However, the art of record for the function of GPV as exemplified by Dong et al. (IDS, Blood, Vol. 89, 1997, pp. 4355-4363), teach that the role of GP Ib-IX-V complex in thrombin's action on the platelet is poorly defined (page 4355).

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In further view of Dong, Kahn et al. Blood, Vol. 94, 1999, pp. 4112-4121, supports the poorly defined role of GPV by producing GPV-deficient mice using gene targeting, wherein the entire GPV gene was knock out. Kahn shows that the mice responded normally to thrombin and tail-bleeding times of wild type and GPV deficient mice were indistinguishable (pages 4114-4115).

In view of the art of record, the claimed invention does not have a credible utility since one skilled in the art would not accept that the recited invention is currently available for use as claimed due to the uncertainty of the role that GP V plays in mammals due to the results displayed by the disclosure and Kahn showing that two transgenic mouse not expressing the GPV gene have different phenotypes. In addition, the claimed invention lacks a substantial utility because of the reasons set forth above. Furthermore, the art of record and the specification display that GPV deficiency in a transgenic mouse does not result or correlate to any disease [e.g. Bernard-Souleir syndrome (BSS)]. The specification fails to provide any transgenic mouse, which could be used in any method of identifying an agent that modulates a biological response to a non-human mammal with a modified GP V gene, which would correlate to treating any disease (e.g. BSS) with an agent. Also for the reasons set forth above it would require further research to identify and reasonably confirm a "real world" use. For example, the transgenic mouse of the claimed invention has a decreased bleeding time compared to a wild type mouse and has a thrombin-induced platelet function at low concentrations of thrombin. A "real world" use is not established by the disclosure because there is not real world use for identifying agents that increase or decrease either characteristic described above and therefore lacks a "Substantial utility" under the following guidelines provided above (A) Basic Research such as studying the properties of the claimed produce itself or the mechanisms in which the material is in involved



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and B) A method of treating an unspecified disease or condition.). In addition, the claimed invention lacks a "well established utility" since the unpredictability of mice with a deficient GP V gene and the poorly defined role of the GP V gene have been supported by the disclosure and the art of record.

Claims 1-27 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by an asserted utility, specific, substantial, or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-27, as best understood, are readable on a genus of a non-human transgenic animal comprising either a modified, a non-functional, or a disrupted glycoprotein (GP) V gene, wherein the genus of the transgenic animal is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 15-20, as best understood, are readable on a genus of a biological response of a non-human transgenic mammal modified GP V gene, wherein the genus of the biological



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response is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 21-22, as best understood, are readable on a genus of a characteristic of an animal that is attributable to the expression of the GP V gene, wherein the genus of the characteristic is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates a genus of transgenic animals, which the GPV gene has been modified so that the animals do not express a functional GPV protein or expresses a GPV protein that demonstrates a reduced functionality as compared with the native or wild type GPV protein (page 1). The specification provides description of a species of a modified mouse GPV gene, which when the non-functional gene is transfected into a cell results in no expression of the GPV protein (pages 14-15).

In addition, the specification contemplates a characteristic between two mammals of the same species, wherein one mammal has for example a wild type GPV gene and the other mammal has a modified GPV gene (page 3). The specification provides sufficient guidance of a species of characteristics from a transgenic mouse with a non-functional GPV gene, which are:

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an increased sensitivity to platelets from the transgenic mouse to activation by low concentrations of thrombin and a decrease bleeding time of the transgenic mouse compared to a wild type mouse. Furthermore, the specification provides sufficient guidance of a species of a biological response from a transgenic mouse with a non-functional GP V gene, which is an increased sensitivity to platelets from the transgenic mouse to activation by low concentrations of thrombin.

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of a biological response of a non-human transgenic mammal modified GP V gene and/or the genus of a non-human transgenic animal comprising a modified or a non-functional GP V gene and/or the genus of a characteristic of an animal that is attributable to the expression of the GP V gene as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a non-human transgenic animal comprising a modified GP V gene or a non-functional GP V gene and/or the genus of a characteristic of an animal that is attributable to the expression of the GP V gene and/or the genus of a biological response of a non-human transgenic mammal modified GP V gene. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which

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is not conventional in the art as of applicant's effective filing date. Claiming a genus of a non-human transgenic animal comprising a modified GP V gene or non-functional GP V and/or a genus of a characteristic of an animal that is attributable to the expression of the GP V gene and/or a genus of a biological response of a non-human transgenic mammal modified GP V gene that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of a non-human transgenic animal comprising a modified GP V and/or a genus of a characteristic of an animal that is attributable to the expression of the GP V gene and/or a genus of a characteristic of an animal that is attributable to the expression of the GP V gene that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

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Claims 1-27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by an asserted utility, specific, substantial, or a well established utility and/or a sufficient written description (for possession of a genus of a non-human transgenic animal comprising a modified or non-functional GP V gene), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. for use in a method for identifying an agent that modulates a biological response of a non-human transgenic mammal having a modified GPV gene and/or a method of determining the effect of an agent on a characteristic of an animal that is attributable to the expression of the GPV gene.

The specification discusses that the invention features a genus of transgenic non-human mammals comprising either a non-functional GPV gene or a modified GPV gene and goes on to contemplate that there are two techniques for producing the transgenic mammals (pages 5-13). The specification provides prior art pertaining to methods for generating transgenic mammals using fertilized eggs and pro-nuclei injection. In addition, the as-filed specification provides the second method for producing transgenic mice, which involves modification of embryonic stem cells using transgenic DNA.

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The specification requires that the starting material, which is a nucleic acid encoding a GPV polypeptide, be used in a method of making a transgenic non-human mammal comprising either a modified or a non-functional GPV gene. The specification provides prior art pertaining to the preparation of transgenic mice that were well known in the art (page 12). For example, a transgene can be introduced into the germline of a transgenic mouse by microinjection for production of a transgenic mouse. The specification displays one method of generating the transgenic non-human mouse: 1) The DNA sequence encoding GPV comprising a coding region of mouse GPV (including the putative initiator Met to Leu<sup>389</sup>) was replaced by a neo cassette and injected the vector into an ES cell line (pages 14-15). The neo clones were identified by positive selection and the clones were injected into embryos from C57BL/6J mice (page 15). Furthermore, the disclosure provides characterization of the effect of GPV gene deletion on thrombin-induced platelet function at low concentrations of thrombin (Example 5, pages 22-23). Furthermore, in example 6, the specification displays the GP V<sup>-/-</sup> mice have a decrease bleeding time in vivo compared to +/+ mice and +/- GPV mice (page 23-24). The specification contemplates that the transgenic mice can be used in a method for identifying agents that modulate a biological response (e.g. thrombotic or pro-thrombotic) (pages 25).

It is further to note that the as-filed specification only contemplates the use of embryonic stem (ES) cell technology or using pro-nuclear injection for the generation of transgenic mammals for used in the claimed invention. See pages 5-13 of the specification. The state of the art at the time application was filed for producing transgenic animals using pro-nuclear injection was considered unpredictable as exemplified by Polejaeva et al. *Theriogenology*, Vol. 53, pages 117-126, 2000, Polejaeva states:

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Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke et al. (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke et al. disclose, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Reprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic mammal comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic mammal other than mice, the state of the art supports that only mouse ES cells were enabled for used in the production of transgenic mice. In view of the

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concerns set forth by the state of the art, the examples do not reasonably address the concerns put forth by the state of the art encompassing any method for producing transgenic mammals for use in addressing the role of GPV or identifying agents that modulate a biological response in the transgenic animal. In view of these factors and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate from the specification and the prior art to any method of producing transgenic mammals comprising a modified GPV gene. However, in view of the concerns stated above encompassing microinjection and random integration into a mammal's genome it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from random integration to determining if a DNA sequence encoding the GPV polypeptide is inserted at the correct site and is expressed at a level sufficient enough to produce a phenotype in any transgenic non-human mammal.

In addition, the disclosure fails to provide any relevant teachings or sufficient guidance with regards to the production of any transgenic mammal comprising a transgenic sequence encoding a modified GPV, which expresses the transgenic sequence such that a phenotype occurs. Furthermore, the as-filed specification fails to describe any particular phenotype exhibited by any transgenic mammal of the invention. Thus, as enablement requires the specification to teach how to make and/or use the claimed invention, the specification fails to enable the production of any transgenic mammal comprising a modified GPV gene.

[Note that although the claimed transgenic mammal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the



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teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic mammal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic mammal would serve if the transgene (e.g. GP V) is not expressed at a sufficient level for a resulting phenotype).]

As the specification fails to provide any relevant teachings or sufficient guidance with regard to the production of a representative number of transgenic non-human mammals as claimed, one skilled in the art would not be able to rely on the state of the art for an attempt to produce any transgenic mammals. This is because of the art of transgenic is not predictable art with respect to transgene behavior and the resulting phenotype. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic mammal comprising a transgene of interest (e.g. GPV); it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For example, the level and specificity of expression of a transgene (e.g. GPV) as well as the resulting phenotype of the transgenic mammal are directly dependent on the specific transgene construct. The individual gene of interest, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of genetically modified animals, which exhibit a particular phenotype. This observation is supported by Wall (Theriogenology, 1996) who states "Our understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine

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(Journal of Biotechnology, 1997) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1<sup>st</sup> paragraph); e.g. specific promoters, presence or absence of introns, etc. The specification does not provide sufficient guidance, and it fails to feature any reasonable correlation between producing transgenic mammal using microinjection of transgene into germ line and producing a transgenic mammal which comprises a transgenic sequence encoding either a modified GPV and which the protein in the transgenic mammal, and, thus, a specific resulting phenotype.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins states that “a given construct may react very differently from one species to another.” See page S39, Summary. Wall et al. report “transgene expression and the physiological consequences of transgene in animals are not always predicted in transgenic mouse studies.” See page 62, first paragraph. Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, because, for example, the cis-acting elements may interact with different trans-acting factors in these other species (page 239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of a representative number of transgenic mammal comprising a modified GPV gene, it would require an undue amount of experimentation to reasonably predict

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the results achieved in any transgenic mammal comprising a transgenic sequence encoding a GPV polypeptide and which expresses the protein in the transgenic mammal at the levels of the claimed product, the consequences of that production, and therefore, the resulting phenotype.

As stated above, the specification provides a transgenic mouse comprising a homozygous disruption of a gene encoding GPV polypeptide in its somatic and germ cells wherein said disruption results in increased sensitivity to of platelets to activation by low concentrations of thrombin and a decrease bleeding time compared to a non-transgenic mouse and a method of making the transgenic mice. However, in addition to the art of record encompassing the unpredictability of producing transgenic mice and the breadth of the claims, the art of record for GP V teaches that the role of GP V is poorly defined (IDS, Dong, pages 4355 and 4362). This is further supported by Kahn (Blood, Vol. 94, 1999, pp. 4112-4121) Kahn produces GPV-deficient mice using gene targeting, wherein the entire GPV gene was knock out and shows that the mice responded normally to thrombin and that the tail-bleeding times of wild type and GPV deficient mice were indistinguishable (pages 4114-4115). In view of Kahn this further supports that the claimed invention is not enabled and it would take an undue amount of experimentation to reasonably extrapolate to any transgenic mouse comprising a non-functional GPV gene wherein a phenotype is an increased sensitivity to platelets to activation by low concentrations of thrombin and a decrease bleeding time compared to any non-transgenic mouse given that there is no evidence showing that the transgenic mouse in the claimed invention is a general phenomenon, and given the doubts expressed in the art of record.

Furthermore, with respect to claims 15-22, which read on an in vivo method for identifying an agent that modulates a biological response of a non human animal comprising a

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non-functional GPV gene, the specification and the state of the art do not provide sufficient guidance for one skilled in the art to monitor any biological response of an agent in an vivo or in vitro assay in said transgenic mammals. The specification and art of record do not provide sufficient guidance for one skilled in the art to reasonably correlate to any in vitro assays or in vivo assays without an undue amount of experimentation. In addition, with respect to claims 21-22, which encompass a method of determining the effect of an agent on a characteristic of a transgenic mouse that is attributable to the expression of the GPV gene, the specification does not provide sufficient guidance for any characteristic of any transgenic mammal. Thus, in view of the breadth of the claim and the lack of sufficient guidance provided by the specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate to any characteristics of said transgenic mammals since no characteristics are enabled by the claimed invention. Therefore it would take an undue amount of experimentation to reasonably correlate to any characteristic of the transgenic mammal that is attributable to the modified expression (mis-expression or no expression) of the GPV gene.

Claims 15-22 are not enabling for a method of identifying an agent that modulates a biological response of a nonhuman transgenic mammal having a modified GP V gene, comprising the step of determining whether an agent that modulates the response or a method of determining the effect of an agent on a characteristic of an animal that is attributable to the expression of the GP V gene. The disclosure states that, "the cells, platelets, tissues, and whole organism of the disclosed transgenic animals specifically have utility in testing the effect of various agents to reduce or increase GPIb-IX-V complex mediated processes (pages 8-9)." It is not apparent from the specification what the steps are required for determining whether an agent

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modulates the response. In view of the lack of sufficient guidance provided by the specification it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the disclosure to make and/or use any method requiring the step of determining whether an agent that modulates the response or a method of determining the effect of an agent on a characteristic of an animal that is attributable to the expression of the GP V gene.

In conclusion, in view of the quantity of experimentation necessary to determine the parameters listed above for the starting material, a transgenic non-human mammal comprising a non-functional, disrupted, or modified GPV gene, the lack of direction or sufficient guidance provided by the as-filed specification for the production of any transgenic non-human mammal, the claimed invention is not enabled. Furthermore, the working examples for the demonstration or the reasonable correlation to the production of any transgenic mammal, in particular when the expression of the GP V gene must occur at a level resulting in a corresponding phenotype, the unpredictable state of the art with respect to the transgene behavior in transgenic non-human mammals of any species, and the breadth of the claims drawn to any transgenic non-human mammal, it would require an undue amount of experimentation for one skilled in the art to make and/or use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 3, 5, and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 3 recites the limitation "the blood plasma of the animal" on line 9, page 27. There is insufficient antecedent basis for this limitation in the claim. There are several kinds of animals well known in the art and the claim does not define, which animal is be referring to.

The term "regenerating" in claims 5 and 16 is a relative term, which renders the claim indefinite. The term "regenerating" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term. Suggest amending the claims to read as follows, "A method of producing a mouse using embryonic stem cells, wherein the somatic and germ cells of said mouse contain a disrupted glycoprotein (GP) V gene, which comprises: (a) introducing a gene construct that disrupts the GP V gene and a selectable marker in mouse embryonic stem cells; (b) identifying and selecting transformed cells having the disrupted GP V gene and the selectable marker; (c) injecting the embryonic stem cells containing the disrupted GP V gene into mouse blastocysts; (d) allowing the embryo to develop producing a chimeric mouse comprising a disrupted GP V gene in its germ line."

The term "determining" in claims 15-22 is a relative term, which renders the claim indefinite. The term "determining" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the term.

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

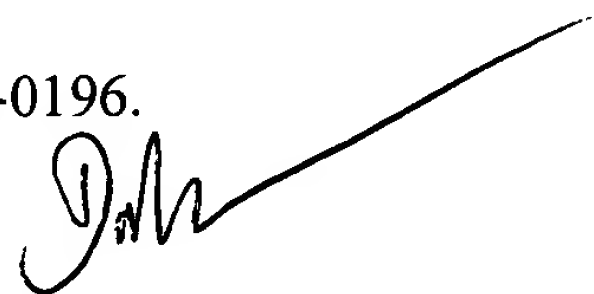
If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman  
Patent Examiner, Group 1635  
January 25, 2001



**DAVE NGUYEN**  
**PRIMARY EXAMINER**



**Attachment for PTO-948 (Rev. 03/01, or earlier)**  
**6/18/01**

**The below text replaces the pre-printed text under the heading, "Information on How to Effect Drawing Changes," on the back of the PTO-948 (Rev. 03/01, or earlier) form.**

**INFORMATION ON HOW TO EFFECT DRAWING CHANGES**

**1. Correction of Informalities -- 37 CFR 1.85**

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the Notice of Allowability. Extensions of time may **NOT** be obtained under the provisions of 37 CFR 1.136(a) or (b) for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

**2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.**

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

**Timing of Corrections**

Applicant is required to submit the drawing corrections within the time period set in the attached Office communication. See 37 CFR 1.85(a).

Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.